Anti-Glc(alpha 1,4)G1c(alpha) IgM antibodies for predict the development of relapsing-remitting multiple sclerosis after the first neurological event

M.S. Freedman, J. Laks, N. Dotan, M. Schwarz, O. Weishaus, A. Dukler, A. Miller, C. Sindic (Ottawa, CAN; Lod, Haifa, IL; Brussels, B)

Background: There is an unmet need to develop specific serum based biomarkers for the diagnosis and prognosis of Relapsing Remitting Multiple Sclerosis (RRMS). Recently the importance of antibodies recognizing glucose-based structures in RRMS patients was emphasized. We have recently reported that elevated levels of serum anti-Glc(alphal ,4)Glc(alpha) (GAGA4) IgM antibodies exist in RRMS patients in comparison to patients with other neurological diseases (OND)1. Others have reported that anti N-glucosylated peptide antibodies are specific for RRMS patients2 however, the predictive value of these antibodies for identifying RRMS patients at the time of first clinically isolated syndrome (CIS) is unknown.

Aim: To evaluate the predictive value of high levels of serum GAGA4 IgM antibodies at CIS for identifying patients that will later be diagnosed as RRMS.

Method: We retrospectively tested frozen sera samples obtained from patients presenting for a diagnostic work-up of CIS. The study included patients that were followed up for at least four years and were confirmed to have RRMS (n=44), and a control group of patients who presented as CIS but were eventually diagnosed as OND (n=44) including inflammatory neurological diseases (OIND, n=23) and other non-inflammatory neurological disease (ONIND, n=21). The RRMS and control groups were matched for gender composition, age and total IgM antibody level. Levels of GAGA4 IgM antibodies in sera samples diluted 1:1200 were measured by enzyme immunoassay and normalized according to the levels of total IgM.

Results: We found significantly higher (p=0.005) levels of GAGA4 IgM antibodies in CIS patients who were eventually diagnosed with RRMS as opposed to OND. Using the OND sample set and a cut-off of mean + 1.3 SD we were able to differentiate between CIS to RRMS vs. CIS to OND with 36% sensitivity, 91% specificity, 80% positive predictive value, and 58.8% negative predictive value.

Conclusion: This is the first report of a serological marker to a glycoconjugate that distinguishes between CIS patients who will evolve to RRMS, and those who turn out to have OND. High levels of IgM antibodies to the GAGA4 epitope seen at the CIS stage are highly specific (>90%) for the future transformation into RRMS. Although MRI can also help to predict RRMS evolution, a serological test is simpler and cheaper. Future studies will examine the correlation of this test with MRI and how well it can predict severity of clinical course.

1 Schwarz et al. Journal of Neuroimmunolgy 154 (2004) 99-110 abstract 325
2 Lolli et al. PNAS July 19, 2005 vol. 102 no. 29 pp 10273-10278